UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,204	02/16/2004	Itzhak Bentwich	050992.0201.03USCP	2203

37808 7590 09/04/2007

ROSETTA-GENOMICS
c/o PSWS
700 W. 47TH STREET
SUITE 1000
KANSAS CITY, MO 64112

EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/708,204	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/2/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 1/31/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/2/07, claims 31-36, 39, 40, 41, and 42 are pending and under examination.

Sequences

The objection to the specification and drawings for lacking SEQ ID NO: identifiers is withdrawn in view of Applicant's amendments thereto, submitted on 7/2/07.

Claim Objections—withdrawn

The objections to Claims 34, 36, 37, 38, 40, and 42 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim are withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejection of Claims 31–42 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of Applicant's amendments to the claims.

Also withdrawn in view of Applicant's amendments to the claims is the rejection of Claims 32, 35, 37, and 38 under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim Rejections - 35 USC § 101 and 112, First Paragraph—maintained

Claims 31-36, 39, 40, 41, and 42 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by a substantial asserted utility.

Response to Arguments

Applicant's arguments have been fully considered and are persuasive in part.

With regard to a specific utility, Applicant argues the application discloses the claimed nucleic acids may be used to regulate expression of Choline Acetyltransferase (ChAT), as shown in Table 7, lines 1468-1501, and Table 8, lines 7124-7275. Accordingly, Applicant submits a specific utility is provided by the

specification with regard to studying the modulation of expression of the ChAT gene.

This argument is persuasive inasmuch as it points to a specific gene that may be regulated and/or detected by the claimed nucleic acids.

With regard to a substantial utility, Applicant points to Table 8, which Applicant states discloses that ChAT encodesthe neurotransmitter acetylcholine and is therefore associated with Alzheimers, and that ChAT is directly implicated with congenital myasthenic syndrome associated with fatal episodes of apnea. Applicant points to Ohno et al., PNAS 98:2017-2022 (2001), which discloses that mutations of the gene ChAT are known to be associated with congenital myasthenic syndrome. Applicant submits that one of ordinary skill in the art would recognize that the claimed polynucleotides may be used to regulate expression (in vitro or in vivo) of ChAT and thereby study the role of this gene in diseases such as Alzheimers and congenital myasthenic syndrome. Accordingly, Applicant respectfully submits that the specification provides a substantial utility for the claimed polynucleotides.

This argument is not persuasive because it amounts to an invitation to do further research using the claimed nucleic acids without any assurance that a real world use will ever emerge from such research.

To satisfy the substantial utility prong, an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230. (The claims at issue in *Fisher* were directed to expressed sequence tags (ESTs), which are short nucleotide sequences that can be used to discover what genes and downstream proteins are expressed in a cell. The court held that "the claimed ESTs can be used only to gain further information about the underlying genes and the proteins encoded for by those genes. The claimed ESTs themselves are not an end of [applicant's] research effort, but only tools to be used along the way in the search for a practical utility) (MPEP 2107.01).

In the instant case, while Ohno et al. teach that ChAt mutations cause disease, Applicant has neither asserted nor shown that the claimed nucleic acids may be used to specifically inhibit any disease-causing ChAT variant. Rather, the asserted substantial utility appears to be based on predicted homology of the claimed nucleic acids to the normal or wild type ChAT gene. It is speculative to presume on the basis of homology to the gene that the claimed nucleic acids may be used to treat or diagnose any particular disease such as myasthenia gravis caused by specific mutations, when the specification provides no evidence showing or suggesting such a use. There is reason therefore to doubt the objective truth of the statement, since one of skill in the art would normally require in vivo, and at the very least, in vitro data showing or suggesting such a utility

for the invention now claimed (MPEP 2107.02, III.A). Further doubt is injected by extrinsic evidence made of record (Krutzfeld et al.), indicating that while bioinformatic analysis of the genome may identify candidate miRNA-like precursor oligonucleotides having possible regulatory functions, bioinformatic predictions are not a guarantee of any particular biological function, nor is there sufficient evidence of record to show that one of skill in the art would accept such bioinformatic data alone, on its face, as sufficient evidence of a substantial function such as that now asserted. See Krutzfeld et al. (previously cited) and Bentwich (2005) *FEBS Lett.* 579:5904-5910, provided herewith.

Absent such evidence, the Examiner submits the claimed nucleic acids have not been researched and understood to the point of providing an immediate, well-defined, real world benefit to the public. The fact that the nucleic acids may be used to inhibit or diagnose the expression of ChAT is, by itself, not a substantial utility, since there is no disclosure teaching one of skill how to use the information derived therefrom for any immediate, real world use aside from general research into gene function.

Therefore, Applicant's arguments of a substantial utility are not persuasive.

With regard to credible utility, Applicant argues one of skill would believe each of the claimed nucleic acids would bind their respective targets based on the disclosure provided by the specification.

To the extent Applicant asserts the claimed nucleic acids are complementary to a specific target gene—in this case, ChAT—the Examiner agrees. A credible utility exists inasmuch as the claimed nucleic acids may be used as probes to detect the expression of a ChAT gene, and possibly, as antisense molecules to inhibit the expression of a ChAT gene.

Accordingly, Applicant's arguments on this point are persuasive.

Nevertheless, the claims remain rejected since they lack a substantial utility.

***

Claims 31-36, 39, 40, 41, and 42 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial utility for the reasons set forth above, one skilled in the art clearly would not be enabled to use the claimed invention for the asserted utility without engaging in undue experimentation.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claims 31, 33, 34, 36, and 39–42 under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (U.S. Patent Application Publication 2005/0059005 A1) is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-36, 41, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Random Primer 24, sold by New England Biolabs (see page 121 of the 1998/99 New England Biolabs Catalog) (New England Biolabs 1998/99 Catalog, cover page, page 121 and 284).

Random Primer 24 contains every possible 24-nucleotide sequence. The following calculations rely on facts provided on page 284 of the catalog, specifically the mass of 1.0 A_{260} unit of single-stranded DNA and the molecular weight of single-stranded DNA per nucleotide (i.e. half the weight of a double-stranded DNA per basepair):

Random 24-mer:

Molecular weight of 24-mer:
24×325 daltons/nucleotide = 7,800 daltons = 7,800 g/mol

Number of possible 24-mers:
$4^{24} = 2.8 \times 10^{14}$ molecules

How many molecules of 24-mer in a vial sold by NEB:
1 A_{260} unit = 33 μg = 3.3×10^{-5} g
3.3×10^{-5} g ÷ 7,800 g/mol = 4.2×10^{-9} mol
$(4.2 \times 10^{-9}$ mol) × $(6.02 \times 10^{23}$ molecules/mol) = 2.5×10^{15} molecules

How many vials needed to sum to 1 of each possible 24-mer:
2.8×10^{14} molecules ÷ 2.5×10^{15} molecules = 0.11 vial

Put another way, every vial of Random Primer 24 sold by New England Biolabs would be expected to contain 9 copies of every possible 24-nucleotide sequence. Therefore, Random Primer 24 would contain every possible gene fragment imaginable that is 24 nucleotides in length, thus meeting the limitations of claim 31 (b) and claims dependent thereon, with regard to the DNA equivalents claimed therein. The reference also meets the limitations of claims 32 and claims dependent thereon to the extent that those claims only modify and further define the embodiment of part (a) of claim 31, but still embrace all embodiments within the scope of part (b) of claim 31. That is claims 32 and 35 encompass DNA sequences of 19 to 140 nucleotides in length comprising sequences equivalent to that shown in SEQ ID NO:15.

The Examiner notes the claims are drawn to an "Isolated nucleic acid." However, no clear or limiting definition of the term "isolated" is readily found in the specification which would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Given the voluminous nature of the instant application, if Applicant is aware of a definition of the term which would preclude compositions of the type referred to in the instant rejection, Applicant is invited to point to such disclosure in replying to the instant rejection.

Accordingly, the Random Primer 24 sold by New England Biolabs anticipates the instant claims.

***

Claims 31-36, 41, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor et al. (US Patent 6,582,908, published as US 2001/0053519 A1 on Dec. 20, 2001).

Fodor et al. taught nucleic acid arrays comprising all possible 20-mers (see claims 4, 7, and 10; and Example 2, beginning at column 22).

Methods for designing and synthesizing "n-mer" arrays to which are attached all possible nucleic acid sequence of a given length, including such calculations as are necessary to design and synthesize all possible oligonucleotides of a given length are taught at columns 17 and 18, for example. For instance, it is said that a 25-mer array would comprise 4^{25} different oligonucleotide sequences.

At column 22, it is taught that at a feature size of 10 μm^2 square micrometers, all possible 10 mers could fit on a single substrate the size of a dime. At a size of 1 μm^2, all possible 20 mers would fit on 100 10 μm^2 substrates. "Thus the present technology provides for making a single substrate of that size having all one million, seven million or more oligonucleotides, depending

on the feature size and the size of the substrate. When the number of desired oligonucleotides is so large that a single substrate is impractical, multiple substrates may be used."

Each of the oligonucleotides present on the array are considered to be isolated to the extent they are isolated in their own particular space on the array.

Accordingly, Fodor et al. taught arrays comprising all possible 20-mers. As such, Fodor et al. taught 20-nucleotide DNA equivalents of the instantly claimed nucleic acids Therefore, Fodor et al. anticipates the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Art Unit 1635
August 22, 2007

/Sean McGarry/
Primary Examiner
AU 1635